22. (New) The composition according to claim 18, wherein said composition contains between 0.1 and 0.2 zinc ion per molecule of said GLP-1 compound.

REMARKS

Claims 14-22 are pending following entry of the above amendments.

In response to the Examiner's request, Applicants submit herewith paper and computer readable forms of a Sequence Listing. In accordance with 37 C.F.R. 1.821 (f), Applicants hereby state that the paper and computer readable copies of the sequence listing are identical.

The amendment to the specification is presented to insert a SEQ ID NO in accordance with the Sequence Listing submitted herewith. As required by 37 C.F.R. 1.121, a "marked-up" copy of the amendment to the specification is appended to this Amendment.

The objection to claim 9 for the misspelling of "cobalt" is rendered moot by the amendments to the claims presented herein.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH

A. ENABLEMENT REJECTIONS

I) The Examiner rejected claims 1-11 because the specification while being enabling for GLP-1 [ie GLP-1 (7-37)], does not provide enablement for GLP-1 compounds. In particular, the Examiner asserts that while "GLP-1 compounds" encompasses analogs and functional derivatives of GLP-1, the specification fails to provide guidance for making, and working examples of, GLP-1 compounds other than GLP-1 (7-37) and that due to the unpredictability in predicting structure, and hence function, from primary amino acid sequence data, "the skilled artisan is left to extensive random trial and error experimentation in order to obtain such GLP-1 compounds other than GLP-1". (Page 5 of Office Action). Applicants respectfully traverse this rejection.

The application teaches that the present invention relates to compounds having GLP-1 like activity (page 3, lines 7-8) where GLP-1 is disclosed to be known to stimulate insulin release (see page 1, lines 19-21). The specification further discloses that the phrase "GLP-1 compounds" includes GLP-1 (7-37) and GLP-1 (7-36) amide and analogues and functional derivatives thereof (sentence bridging pages 1-2) and teaches on page 3, lines 9-18 that "Examples of specific GLP-1 compounds are polypeptides comprising the 7 - 34 amino acid sequence of GLP-1, viz. formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys

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or a peptide sequence derived from formula I without eliminating the GLP-1 like activity. The term GLP-1 compound also comprises derivatives of said polypeptides such as acid addition salts, carboxylate salts, lower alkyl esters, amides, lower alkyl amides and lower dialkyl amides."

The present application also teaches on pages 3-4 how to use such GLP-1 compounds to produce compositions which exhibit a protracted release of the GLP-1 compound as measured for example in the absorption assay described in the last paragraph of page 6 of the application. Thus, the application teaches how to obtain GLP-1 compounds other than GLP-1 (7-37) and how to use such compounds to produce the protracted release compositions of the present invention.

Moreover, in determining whether the specification would have enabled one skilled in the art as of the 1994 Danish priority filing date to "obtain such GLP-1 compounds other than GLP-1", one must also consider the state of the prior art at that time since it is well settled that "[A] patent need not disclose what is well known in the art" [In re Wands 8 USPQ 2d 1400, 1402 Fed. Cir. 1988)] and "preferably omits that which is well-known to those skilled and already available to the public" [MPEP 2164.05 (a)]. Here, the prior art as of 1994 is replete with disclosure of various GLP-1 analogs and derivatives having GLP-1 like activity as well as methods for preparing such compounds for use in the present invention (see, for example, US patents 5, 545,618, 5,188,666 and 5,120,712). Accordingly, in view of the above, Applicants submit that the present application clearly enables one skilled in the art to obtain GLP-1 compounds other than GLP-1 (7-37) for use in producing the protracted compositions of the present invention without undue experimentation and withdrawal of the section 112, first paragraph rejection is therefore respectfully requested.

II) The Examiner rejected claim 7 because the specification does not provide enablement for a composition where the thixotropic property only or mainly results from GLP-1. In response, Applicants respectfully submit that this rejection is rendered moot by the cancellation of claim 7 herewith.

III) The Examiner, citing to In re Mayhew [188 USPQ 356 (CCPA 1976)] rejected claims 1-11 as being nonenabled on the basis that while the specification discloses that compositions comprising GLP-1 and a phenolic compound in "certain" concentrations form

thixotropic gels, these concentrations are not included in the claims. In particular, the Examiner asserted that "all of the working examples wherein a thixotropic gel is formed contain GLP-1 and a phenolic compound or GLP-1, a phenolic compound, and zinc in 'certain' concentrations but these concentrations are not included in the claims" (page 7 of Office Action). Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner's assertion that the claims be limited to the concentrations recited in the working examples. As the predecessor court to the Federal Circuit noted in In re Goffe, in determining whether an unclaimed feature is critical, the entire disclosure must be considered and features that are merely preferred are not critical 191 USPQ 429, 432 (CCPA, 1976).

Here, while the application does disclose that the compositions of the invention are to contain a GLP-1 compound and a phenolic and /or alcoholic aromatic compound in "certain concentrations", the application teaches that the compositions can be prepared by using the GLP-1 compound in a concentration within certain ranges (page 4, lines 8-13); for example, compositions containing not less than about 10 mg/ml of a GLP-1 compound. The application also discloses that "the invention is further illustrated by the following examples which are not to be construed as limiting but merely as an illustration of some preferred features of the invention" (page 5, lines 4-6, emphasis added) where the examples provide formulations containing a specific concentration of GLP-1 (20 mg/ml). Thus, it is Applicants' position that the concentrations recited in the Examples are preferred features that need not be included in the claims.

Moreover, the case cited by the Examiner (In re Mayhew) actually supports Applicants' position that the concentrations of the components of the compositions recited in the examples need not be included in the claims. Specifically, in Mayhew, of the four grounds of rejection considered by the CCPA, only the third ground of rejection was relevant to the present application; namely that neither the temperature range in the claimed cooling zone nor its function was recited in the claims (188 USPQ at 357). In Mayhew, the CCPA reversed this ground of rejection on the basis that since the general function of the cooling zone is clear, selection of the temperature of the zone would be within the ability of one of ordinary skill in the art attempting to follow the teaching of the specification.(Id at 359).

Here as in Mayhew, the function of the claimed compositions is clear (to delay the release of the GLP-1 compound, see page 3, lines 4-5 of the specification) and whether a composition exhibits the claimed function can readily be determined via the absorption assay described in the last paragraph of page 6 of the specification. In addition, as noted above, the application provides preferred concentrations of the components which may be included in the compositions of the invention. Accordingly, Applicants submit that here as in Mayhew, the selection of concentrations which would produce a composition which exhibits a protracted release of the GLP-1 compound is well within the ability of one of ordinary skill in the art attempting to follow the teaching of the specification. Applicants therefore respectfully request withdrawal of this rejection.

B. WRITTEN DESCRIPTION REJECTION

The Examiner rejected claims 1-11 as containing subject matter which was not described in the specification in such a way as to reasonably convey that the skilled person had possession of the claimed invention at the time the application was filed. In particular, the Examiner asserts that while the claims are directed to GLP-1 compounds and the specification intends for GLP-1 compounds to encompass analogs and functional derivatives of GLP-1, the specification and claims do not indicate what distinguishing attributes are shared by members of the genus. With all due respect, Applicants disagree.

The present application discloses that the invention relates to GLP-1 compounds having GLP-1 like activity [where GLP-1 is disclosed to be known to stimulate insulin release (see page 1, lines 19-21 of the specification)] and that GLP-1 compounds bind to the GLP-1 receptor (page 3, lines 7-9). Thus, "GLP-1" compounds share the common attribute of binding to the GLP-1 receptor and stimulating insulin release.

Moreover, as noted above, the specification discloses that the phrase "GLP-1 compounds" includes GLP-1 (7-37) and GLP-1 (7-36) amide and analogues and functional derivatives thereof (sentence bridging pages 1-2) and teaches on page 3, lines 9-18 that "Examples of specific GLP-1 compounds are polypeptides comprising the 7 - 34 amino acid sequence of GLP-1, viz. formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys

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or a peptide sequence derived from formula I without eliminating the GLP-1 like activity. The term GLP-1 compound also comprises derivatives of said polypeptides such as acid addition salts, carboxylate salts, lower alkyl esters, amides, lower alkyl amides and lower dialkyl amides."

Accordingly, Applicants submit that the specification reasonably conveys to one skilled in the art what distinguishing attributes were shared by the genus of "GLP-1 compounds" and withdrawal of this rejection is therefore respectfully requested.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112 SECOND PARAGRAPH

The Examiner rejected the claims under section 112 second paragraph on the following grounds:

1) claims 3 and 11 recite an improper Markush format;

2) the lack of antecedent basis for "wherein the thixotropic property" in claims 7 and 8;

3) the use of the phrases "preferably", "more preferably" and "most preferably" in claims 3, 6, 9 and 11;

4) the recitation of the term "gel" in claims 1 and 3-11 because the specification allegedly does not identify the material element or combination of elements which is definitive of "gel";

5) the recitation of "between 0.2 and above 0.1" in claim 11;

6) the recitation of "GLP-1 compound" in claim 11 as indefinite because the "specification does not identify that material element or combination of elements which is unique to, and, therefore definitive of 'GLP-1'"(page 9 of Office Action); and

7) the use of the term "mainly" in claims 7 and 8.

Applicants respectfully traverse these rejections and address each of them in turn below:

1-3, 5 and 7) are rendered moot by the amendments to the claims presented herein.

4) the specification clearly identifies the combination of elements definitive of "gel" as a GLP-1 compound and a phenolic or alcoholic aromatic compound (page 3, lines 20-22).

6) the recitation of "GLP-1 compound" does have a clear and definite meaning as the specification does disclose that the invention relates to GLP-1 compounds having GLP-1 like activity [where GLP-1 is disclosed to be known to stimulate insulin release (see page 1, lines 19-21 of the specification)] and that GLP-1 compounds bind to the GLP-1 receptor (page 3, lines 7-9).

Accordingly, in view of the above amendments and remarks, Applicants respectfully request withdrawal of the section 112 second paragraph rejections.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 102(b)

The Examiner rejected claims 1-11 as being anticipated by Danley EP 619322 in view of Nairn and Ballard. In particular, the Examiner cites to the following four separate compositions in Danley:

1) Example 34 (1-8 mg/ml of GLP-1 + zinc in a 1:1 to 270:1 molar ratio of zinc to GLP-1)
2) Example 21 (4mg/ml GLP-1 + 2.44 mg/ml phenol)
3) Table 3 on page 37 (9.5 mg GLP-1 + polyethylene glycol)
4) Disclosure on page 12, line 57 to page 14, line 9 as disclosing a composition of 4 mg/ml GLP-1 (7-37), phenol and zinc

and concludes that although Danley is silent with respect to the composition being a gel, the specification does not identify that element or a combination of elements which is definitive of a gel (citing to Nairns as evidence that there is no single definition for the term gel) and since Danley's composition "has all the ingredients of the claimed composition", the "thixotropic properties of such compositions only or mainly result from the presence of the GLP-1 compound in the absence of evidence to the contrary" (page 11 of Office Action).

Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that the specification clearly identifies the combination of elements definitive of "gel" as used in the present application as a GLP-1 compound and a phenolic or alcoholic aromatic compound (see, for example, page 3, lines

20-22) and that newly added independent claim 14 is directed to a composition which comprises not less than about 10 mg/ml of a GLP-1 compound and a phenolic or alcoholic aromatic compound. The specification and the newly added dependent claims 17-22 further disclose that a divalent metal ion such as zinc may be added to the composition.

By comparison, the compositions of Example 34 of Danley and in Table 3 of Danley do not contain a phenolic or alcoholic aromatic compound and the composition of Example 21 and that referred to by the Examiner as item 4 above contain 4 mg/ml GLP-1, ie less than 10 mg/ml GLP-1 (in addition, the disclosure cited to by the Examiner on page 12 line 57 to page 14, line 9 as disclosing a composition of GLP-1 (7-37), phenol and zinc further discloses that the composition is to contain a basic polypeptide such as protamine).

Accordingly, as none of the compositions of Danley cited to by the Examiner contain not less than about 10 mg/ml of a GLP-1 compound and a phenolic or alcoholic aromatic compound, Danley cannot be held to anticipate the claimed invention and withdrawal of the section 102 rejection is respectfully requested.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 103

The Examiner rejected claims 1-11 under section 103 as being unpatentable over Danley in view of Nairns (no single art recognized definition of the term "gel") and Ballard and further in view of Galloway, Schott and Ballard. Galloway was cited as teaching that only a small quantity of zinc is required to complex with and precipitate a significant portion of GLP-1 molecules; Schott as teaching that thixotropy is particularly useful in the formulation of pharmaceutical suspensions and emulsions and Ballard as giving a clear indication of success in designing a prolonged action preparation with thixotropic pellets. The Examiner concludes that while Galloway, Schott and Ballard do not teach a thixotropic composition comprising GLP-1, it would have been obvious to make a composition as taught by Danley and to modify that teaching by making a thixotropic composition as taught by Schott and/or Ballard with a reasonable expectation of success. Applicants respectfully traverse this rejection.

As discussed above, the present specification clearly identifies the combination of elements definitive of "gel" as a GLP-1 compound and a phenolic or alcoholic aromatic compound (page 3, lines 20-22) and newly added independent claim 14 is directed to a composition

which comprises not less than about 10 mg/ml of a GLP-1 compound and a phenolic or alcoholic aromatic compound.

By comparison, Danley discloses solutions and aqueous suspensions containing GLP-1 but contains no mention of gel formation. Moreover, as discussed above, none of the compositions of Danley cited by the Examiner contain not less than about 10 mg/ml of a GLP-1 compound and a phenolic or alcoholic aromatic compound.

The newly cited secondary references of Galloway, Schott and Ballard do not remedy the deficiencies of Danley as Schott and Ballard merely disclose the use of thixotropy in the production of pharmaceutical formulations and Galloway teaches the production of complexes of a GLP-1 molecule with a divalent metal ion. None of these references, either alone or in combination with Danley, either teaches or suggests the presently claimed invention; ie a composition comprising not less than about 10 mg/ml of a GLP-1 compound and a phenolic or an alcoholic aromatic compound, where said composition is a gel having thixotropic properties. Accordingly, withdrawal of this obviousness rejection is respectfully requested.

In view of the above amendments and remarks, Applicants respectfully submit that this application is in condition for allowance and early and favorable action by the Examiner to that end is solicited.

Respectfully submitted,

Date: January 15, 2003

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"Marked-Up" Copy Of Amendment To The Specification

Please replace the paragraph at page 3, lines 7-18 with the following paragraph:

--This invention deals with compounds having GLP-1 like activity herein referred to as GLP-1 compounds. GLP-1 compounds bind to the GLP-1 receptor (vide Proc.Nat. Acad.Sci.USA 89 (1992), 8641). Examples of specific GLP-1 compounds are polypeptides comprising the 7 - 34 amino acid sequence of GLP-1, viz. formula I (SEQ ID NO:1):

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys

(I)

or a peptide sequence derived from formula I without eliminating the GLP-1 like activity. The term GLP-1 compound also comprises derivatives of said polypeptides such as acid addition salts, carboxylate salts, lower alkyl esters, amides, lower alkyl amides and lower dialkyl amides.--